# Early fistulography can predict whether biochemical leakage develops to clinically relevant postoperative pancreatic fistula

Yoshinori Takeda, MD[a,b], Akio Saiura, MD, PhD[a,b], Yosuke Inoue, MD, PhD[a], Yoshihiro Mise, MD, PhD[a,b], Takeaki Ishizawa, MD, PhD[a], Yu Takahashi, MD, PhD[a], Hiromichi Ito, MD[a]

[a]Department of Hepatobiliary and Pancreatic Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Ariake, Tokyo, Japan

[b]Department of Hepatobiliary-Pancreatic Surgery, Juntendo University School of Medicine, Hongo, Tokyo, Japan

**Corresponding author:** Akio Saiura, MD, PhD
Department of Hepatobiliary-Pancreatic Surgery, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
E-mail: a-saiura@juntendo.ac.jp
Tel: +81-3-3813-3111
Fax: +81-3-3818-7589

**Short title:** Fistulography and CR-POPF

**Keywords:** Fistulography, biochemical leakage, clinically relevant postoperative pancreatic fistula

**Funding:** None

**Conflicts of interest:** The authors declare that they have no conflict of interest.

**Meeting presentation:** This study was presented in part at the 118th Annual Congress of Japan Surgical Society, April 5-7, 2018 in Tokyo, Japan.

**Word count:** 2716 words

**Abstract**

**Background:** As complete prevention of postoperative pancreatic fistula (POPF) after pancreatic surgery remains difficult, many risk factors of clinically relevant POPF (CR-POPF) have been reported. However, their clinical impact could be limited because all previous reports included patients without biochemical leakage (BL) that rarely developed to CR-POPF. Therefore, a new strategy for identifying high-risk patients who develop delayed complications from patients with confirmed BL and for implementing interventions for such patients in the early postoperative period is required. This study aimed to examine the role of fistulography in predicting CR-POPF from confirmed BL.

**Methods:** Consecutive patients diagnosed with BL on postoperative day 3 after pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) from January 2013 to June 2015 in our institution were included. Fistulography was performed 1 week after the operation, and the associations between findings on fistulography and delayed complications associated with POPF were evaluated.

**Results:** Eighty-four (37%) of 227 patients who underwent PD and 45 (48%) of 94 patients who underwent DP were included and divided to two groups according to fistulographic findings (simple type, n=107, 83%; cavity type, n=22, 17%). The latter finding was associated with a greater morbidity rate (Clavien-Dindo grade ≥2: 36% vs 59%, $p$=0.018) and a worse final POPF grade (B/C 64% vs 95%, $p$=0.003). In the multivariate analysis, cavity type on fistulography was a significant predictive factor for grade B/C POPF.

**Conclusions:** Fistulography is a useful examination for identifying patients with a high-risk of developing delayed complications associated with POPF.

## Introduction

With improvements in perioperative surgical and medical management, postoperative mortality rates for pancreatectomy have greatly decreased [1, 2]. However, postoperative morbidity remains high, and postoperative pancreatic fistula (POPF) remains a difficult complication of pancreatic surgery. Despite many proposed interventions to prevent leakage from pancreatic anastomosis or the resection stump, the incidence of pancreatic leakage including biochemical leakage (BL) and clinically relevant postoperative pancreatic fistula (CR-POPF) remains high (38%-50%) [3, 4].

Although most patients with BL can recover uneventfully as long as the leaked pancreatic fluid is adequately drained, some can develop CR-POPF with serious complications, such as abscess and life-threatening arterial bleeding [5-7]. Patients with CR-POPF had prolonged length of hospital stay (LOS) and increased incidence of readmission, which were associated with increased medical cost and might hamper the induction of subsequent therapy [4, 8, 9]. Moreover, readmission was reported to be associated with higher 90-day mortality rates [10, 11] and poor long-term survival rate from malignant disease [12]. Therefore, to mitigate the clinical effect of currently unpreventable POPF, identifying patients with a high risk of developing serious consequences as early as possible is important. Although many risk factors of CR-POPF have been reported [13, 14], they could have limited clinical impact in postoperative management because their studies included patients without BL that rarely develop to CR-POPF. To be more effective, risk factors of CR-POPF are desirable to be determined among patients who were already confirmed to have BL.

Fistulography is an effective diagnostic and therapeutic intervention for POPF [15-17]. This technique is a noninvasive, cheap, and readily available dynamic

diagnostic test. Faccioli et al. reported that fistulography helped in confirming clinically suspected POPF and in detecting drain migration into intraluminal position [17]. In our institution, we perform fistulography routinely on a weekly basis for patients with BL to evaluate leakage. Herein, we hypothesized that fistulography is useful for predicting the risks of late complication associated with POPF in the early phase of the postoperative period. This study aimed to examine the role of fistulography in predicting CR-POPF in patients with confirmed BL.

## Materials and Methods

### *Patients and Diagnosis of POPF*

We retrospectively analyzed the medical records of our patients who underwent pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) from January 2013 to June 2015 at the Cancer Institution Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan. All operations were performed or supervised by A.S. or Y.T. Patients who underwent total pancreatectomy, middle pancreatectomy, or enucleation were excluded. Fistulography was performed 1 week after operation in patients diagnosed with BL on postoperative day (POD) 3 according to the International Study Group of Pancreatic Fistula (ISGPF) definition [5]. The data retrieved from the medical records included patients' demographics, diagnosis for pancreatectomy, postoperative laboratory test results, findings of fistulography, and postoperative complications. The overall incidence, severity, morbidity, and mortality of POPF were evaluated for 90 days after the index operation. This study was approved by the Institutional Review Board (2016-1072).

***Operative Procedure and Postoperative Management***

The details of the PD were described previously [18]. Pancreatic anastomosis was performed by standard duct-to-mucosal, end-to-side pancreaticojejunostomy. An external plastic stent was routinely placed over the anastomosis, and one or two closed drain(s) with a diameter of 8 mm were placed depending on the operator's decision. The first drain was placed through the foramen of Winslow, and an additional drain was sometimes placed at the superior edge of the pancreaticojejunostomy. The details of the DP were also described previously [19]. The pancreas was typically transected with a staple device, and the main pancreatic duct was over-sewn if possible. A single closed suction drain with a diameter of 8 mm was placed near the stump of the remnant pancreas. Patients were discharged home when all drains were removed and they had stable general conditions and sufficient oral intake.

***Drain Management and Inclusion Criteria of Fistulography***

The drain managements were not different between PD and DP. The drainage fluid was sent to the laboratory, and amylase levels were measured daily from POD 1. The drain was removed on POD 4 if the amylase levels in the drainage fluid on POD 3 were within three times the upper limit of normal serum amylase values. Otherwise, the drain was kept in place and managed conservatively. The drains were maintained on closed suction unless the drainage output was contaminated. Drainage output was cultured weekly, which helped in the administration of appropriate antibiotics when the patient had signs of infection. The amount of drain output was assessed every day, and fistulography was routinely performed at POD 7 and repeated weekly. The drains were removed when the drain output was completely dried up and the fistula tract was

confirmed to have no residual space by fistulography. When the patient developed fever or other signs of infection, abdominal computed tomography (CT) was performed to rule out an intra-abdominal abscess. Parenteral antibiotics and percutaneous additional drain placement were considered in case of an undrained abscess.

***Procedure of Fistulography***

All fistulographies were performed by surgical teams in the radiology suite. The drain was pulled over the guide wire and 3–5 mL of water-soluble contrast (Urografin®; Beyer, Osaka, Japan) was gently injected into the fistula tract via a smaller catheter (7-Fr Atom versatile tube®; Atom Medical, Saitama, Japan) under fluoroscopy. Following tract visualization, the extent of the fistula was determined using a low pressure of contrast medium. A soft drain (8-Fr Phycon Oxygen Cathetel®; Fuji Systems, Tokyo, Japan) was placed over the guide wire into the same position as the initial drain. The location of the pancreatic anastomosis and cut-edge was detected by the change in the diameter of the pancreatic stent or staple. The weekly routine fistulography was not accounted as an interventional procedure because it was only for the assessment of the fistula. Additional fistulography and repositioning of drains in patients with any sign of infection such as fever or elevated inflammation response were accounted as percutaneous intervention therapy.

***Classification of Findings on Fistulography***

The injected contrast medium filled the tract around the drain, and we evaluated the extent of the fistula cavity near the pancreatic anastomosis or stump. Based on the findings of fistulography, the fistula was classified into two types: simple

and cavity. Figure 1 shows the representative fistulographic images for these two types. The simple type was defined as a mature tract with or without minimal spillage of contrast medium around it (Figure 1a and b). The cavity type was defined as immature pooling of contrast medium outside of the drainage tract (Figure 1c and d).

### *Statistical Analysis*

Data are shown as frequencies with percentages or median with ranges. Categorical variables were compared by the chi-square test and continuous variables were compared using the Mann-Whitney U test. Variables with $p<0.1$ were entered into the logistic regression analysis. A $p$ value <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics version 22 (IBM, Armonk, NY, USA).

## Results

### *Demographics of Patients with POPF*

Among 321 consecutive pancreatectomies (227 PDs and 94 DPs), 129 patients (40%; after PD, 84 patients [37%]; after DP, 45 patients [48%]) had BL on POD 3. The demographics of the patients are shown in Table 1. Among patients who underwent PD, 28 (12%) were diagnosed with BL, 55 (24%) with grade B POPF, and 1 (0.4%) with grade C POPF. Among 55 patients with grade B POPF, 31 (56%) received prolonged drain placement only, 24 (44%) received pharmacologic treatment with or without prolonged drain placement, and 14 (25%) received interventional therapy including drain repositioning. After DP, 12 patients (13%) were diagnosed with BL, 32 patients (34%) with grade B POPF, and 1 patient (1.1%) with grade C POPF. Among 32

patients with grade B POPF, 18 (56%) received prolonged drain placement only, 14 (44%) received pharmacologic treatment, and 6 (19%) received interventional therapy including endoscopic nasopancreatic drain. Overall, 10 patients (3.1%) required additional percutaneous or operative interventions for POPF-related intraabdominal abscess or bleeding. Pseudoaneurysm occurred in one patient and angiographically embolized. No patient died from POPF-associated complications. Although pancreatic cancer was the most common indication for pancreatectomy (64 patients, 50%), the majority had soft glands and a small main pancreatic duct (<3 mm).

***Comparison of the Cavity and Simple Types of POPF in Initial Fistulography***

Initial fistulography was obtained on approximately POD 7 (4–11 days). Fistulography successfully showed the image in all cases, and no fistulography-related complication occurred. Among 84 patients who underwent PD, 72 (86%) were classified as simple type and 12 (14%) as cavity type based on the initial fistulographic findings. After DP, 10 patients (22%) were classified as simple type and 35 patients (78%) as cavity type based on the initial fistulographic findings. The characteristics of patients with each type are shown in Table 2. The connection between drain and pancreatic duct was not shown in any of the cases. The drain fluid was amylase-rich (median, 1190 IU/L) despite fistulographic findings of a simple tract without any spillage to the pancreatic anastomosis or pancreatic stump (Figure 1a). All drains were removed after fistulographic confirmation of a matured tract regardless of the initial fistulographic findings.

All patients who had cavity type after PD developed CR-POPF, whereas among those who had cavity type after DP, 9 (90%) developed CR-POPF ($p$=0.455).

Patients with cavity-type leakage developed severe complications associated with POPF significantly more frequently than those with simple-type leakage with regard to abscess treated with a percutaneous drain ($p$=0.002). When the quality metrics for the entire hospital course of those patients were compared, patients with cavity-type leakage had more complications of Clavien-Dindo ≥grade 2 ($p$=0.018) and longer postoperative hospital stay ($p$=0.006) than those with simple-type leakage. The incidence of reoperation or 90-day mortality was not significantly different between the two groups (both $p$=1.000).

***Risk Factors of Grade B/C POPF***

We evaluated the risk factors associated with POPF-associated late (after POD 7) complications in patients with amylase-rich drainage output on POD 3. One patient with simple-type leakage who received antibiotics therapy before POD 7 due to pancreatic leakage–associated abscess was included. The univariate analysis showed that male sex, C-reactive protein levels on POD 7 >6 mg/dL, and cavity type by fistulography on POD 7 were associated with a final grade of B or C for the classification of the severity of fistulas (Table 3). In the multivariate analysis, male sex and cavity-type findings on initial fistulography remained significant risk factors (Table 4).

**Discussion**

We investigated the role of fistulography in predicting the risk of developing severe late complications related to pancreatic fistula, and results showed that if fistulography reveals a cavity-type leakage on POD 7, the patient has 13 times greater

chance of developing complications associated with POPF in the later recovery course from pancreatic surgery.

Although risk factors for CR-POPF have been reported, they had limited clinical impact on outpatient management of pancreatic leakage. Callery et al. [14] proposed the Fistula Risk Score for predicting the risk of CR-POPF after PD. This score is based on multiple factors, including gland texture, pathology of the disease, the pancreatic duct, and intraoperative blood loss, and has validated predictive ability using independent prospective data from multiple centers. However, its value in predicting the development from BL to CR-POPF might be limited, because most patients who develop CR-POPF have a soft gland and small pancreatic duct, similar to our cohort. Moreover, a large study from Western countries could not develop a risk score model after DP, which also supported the difficulty in predicting the risk of CR-POPF among patients who had pancreatic remnant with soft gland texture [13]. Actually, established risk factors such as high Fistula Risk Score and high amylase value in drains were not significant in the present study.

Conversely, fistulographic findings in the early phase after operation were the strongest predictor for delayed complications for patients with already confirmed BL regardless of the type of procedure. Thus, we can modify the clinical pathway according to the fistulographic findings, resulting in decreased LOS and readmission rate. It is currently difficult to determine the optimal timing for discharge. In Japan, conservative management prolongs LOS to avoid severe complication associated with CR-POPF [20] because mortality rate as high as 5%-13% was reported in patients with CR-POPF [4, 21]. Meanwhile, developing CR-POPF was the main reason for 30-day readmissions in Western countries [10] and the high readmission rate in patients who were discharged

with drain placement for pancreatic leakage, suggesting difficulty in outpatient management [22]. According to our results, we recommend that patients with simple-type leakage can be discharged with drains if they are clinically stable, whereas patients with the cavity-type leakage should stay longer in the hospital for close monitoring or have more intensive follow-ups in the clinic if they are discharged with the drain. This strategy could shorten the LOS in Japan without the risk of life-threatening complications associated with CR-POPF and decrease the readmission rate in Western counties by preventing delayed diagnosis of complications without prolonged length of stay [4].

Although CT is used for routine examination after pancreatectomy in several institutions [23, 24], fistulography has some advantages. First, fistulography could show the space where no fluid has pooled, whereas CT shows fluid collection. Fistulography retrogradely visualizes the maturation of pancreatic leakage, which is affected by factors such as degree of leakage, patients' systemic conditions, and infection. Simple-type leakage would be revealed when the leakage is mature, whereas cavity-type leakage would be revealed when the leakage was immature. Patients with cavity-type leakage possibly develop CR-POPF because immature leakage likely enlarges its area in the late phase after pancreatectomy, resulting in inadequate drainage or infection. Meanwhile, CT detects fluid collection, making it difficult to detect leakage maturation among patients with well-functioning drainage. Second, CT is inferior to fistulography as a routine examination from the viewpoint of cost and radiation exposure [25]. The possibility that fistulography itself could cause or contribute to CR-POPF development is low, because no fistulography-related complication occurred and the rate of patients who required pharmacologic or interventional therapy was similar with that of a

previous report [4]. Such treatments were provided in 42 (13.1%) of 321 patients who underwent PD or DP in this study period, whereas Maggino reported a rate of 13.2% in a large multicenter study [4].

Male sex was also identified as an independent risk factor to grade B/C POPF in our study. One possible reason for this unexpected finding is that male sex was a surrogate indicator of a fatty pancreas which has been reported to influences the risk of POPF in a previous study [26].

The present study has some limitations. First, this was a single-institution retrospective study, and prospective data would be needed to validate whether our classification could predict CR-POPF among patients with confirmed BL and whether postoperative management based on our fistula classification could decrease LOS without increasing readmission rate. Some established risk factors for POPF such as soft remnant pancreas and high amylase value in drain were not significant in our analysis, which might be due to the low number of patients. Nevertheless, the present study demonstrated the strong impact of fistulography in predicting grade B/C POPF. Knowing the initial fistulographic result might prolong the duration of drain placement and hospital stay. However, our objective criteria in drain removal minimized the subjective bias. Second, we had a higher CR-POPF rate compared with Western countries [3, 27]. Our strict policy of drain management using fistulography prolonged the length of drain placement, which makes POPF severity grade, based on ISGPF classification, appear worse. However, more than half of our patients with grade B POPF did not require any medical intervention other than prolonged drain placement, which resulted in less severe complications, as reported in a recent study [4]. Lastly, there is a technical caveat for the effective use of fistulography: placing the drainage

tube with its tip as closely as possible to the pancreatic anastomosis or stump for effective drainage and keeping the tract as short and straight as possible for later manipulation over fistulography are critical. If the drain placed is steeply curved or coiled intraperitoneally, reinsertion of the tube over the guide wire after fistulography may be difficult or impossible. Besides, insertion of a tube over the guide wire can be easily carried out by surgeons, unlike percutaneous puncture or placement of new drain [28]. Therefore, we recommend to routinely perform fistulography in patients with BL because of its excellent prediction ability of developing CR-POPF. The diagnostic application of fistulography might be limited in cases with postoperative encapsulated pseudocyst and/or if drains are placed far from the pancreatic anastomosis or stump. In such situations, fistulography might incorrectly show simple-type leakage despite the presence of severe pancreatic leakage. The misdiagnosis as simple-type may explain the high rate of grade B/C POPF in simple-type. Therefore, follow-up is required even if patients who were diagnosed as simple-type, and work-up should be performed when they had any signs of infection.

In conclusion, fistulography is a useful examination for managing pancreatic leakage. Our novel classification based on the findings of fistulography on POD 7 can effectively predict patients with a high risk of developing later complications and guide management to mitigate the consequences of those complications.

**Acknowledgments:** None

## References


1. Gouma DJ, van Geenen RC, van Gulik TM, et al (2000) Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Annals of surgery 232:786-795
2. Sanchez-Velazquez P, Muller X, Malleo G, et al (2019) Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons. Annals of surgery
3. Van Buren G, 2nd, Bloomston M, Schmidt CR, et al (2017) A Prospective Randomized Multicenter Trial of Distal Pancreatectomy With and Without Routine Intraperitoneal Drainage. Annals of surgery 266:421-431
4. Maggino L, Malleo G, Bassi C, et al (2019) Decoding Grade B Pancreatic Fistula: A Clinical and Economical Analysis and Subclassification Proposal. Annals of surgery 269:1146-1153
5. Bassi C, Marchegiani G, Dervenis C, et al (2017) The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 161:584-591
6. Malleo G, Pulvirenti A, Marchegiani G, et al (2014) Diagnosis and management of postoperative pancreatic fistula. Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie 399:801-810
7. Yekebas EF, Wolfram L, Cataldegirmen G, et al (2007) Postpancreatectomy hemorrhage: diagnosis and treatment: an analysis in 1669 consecutive pancreatic resections. Annals of surgery 246:269-280
8. Yoshioka R, Yasunaga H, Hasegawa K, et al (2014) Impact of hospital volume on hospital mortality, length of stay and total costs after pancreaticoduodenectomy. Br J Surg 101:523-529
9. Kent TS, Sachs TE, Callery MP, et al (2011) Readmission after major pancreatic resection: a necessary evil? Journal of the American College of Surgeons 213:515-523
10. Fong ZV, Ferrone CR, Thayer SP, et al (2014) Understanding hospital readmissions after pancreaticoduodenectomy: can we prevent them?: a 10-year contemporary experience with 1,173 patients at the Massachusetts General Hospital. J Gastrointest Surg 18:137-144; discussion 144-135
11. Chen Q, Bagante F, Olsen G, et al (2019) Time to Readmission and

Mortality Among Patients Undergoing Liver and Pancreatic Surgery. World J Surg 43:242-251

12. Schneider EB, Hyder O, Wolfgang CL, et al (2012) Patient readmission and mortality after surgery for hepato-pancreato-biliary malignancies. Journal of the American College of Surgeons 215:607-615

13. Ecker BL, McMillan MT, Allegrini V, et al (2019) Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group. Annals of surgery 269:143-149

14. Callery MP, Pratt WB, Kent TS, et al (2013) A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. Journal of the American College of Surgeons 216:1-14

15. Hirota M, Kanemitsu K, Takamori H, et al (2008) Percutaneous transfistulous pancreatic duct drainage and interventional pancreatojejunostomy as a treatment option for intractable pancreatic fistula. American journal of surgery 196:280-284

16. Molinari E, Bassi C, Salvia R, et al (2007) Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. Annals of surgery 246:281-287

17. Faccioli N, Foti G, Molinari E, et al (2012) Role of fistulography in evaluating pancreatic fistula after pancreaticoduodenectomy. Br J Radiol 85:219-224

18. Inoue Y, Saiura A, Yoshioka R, et al (2015) Pancreatoduodenectomy With Systematic Mesopancreas Dissection Using a Supracolic Anterior Artery-first Approach. Annals of surgery 262:1092-1101

19. Yoshioka R, Saiura A, Koga R, et al (2010) Risk factors for clinical pancreatic fistula after distal pancreatectomy: analysis of consecutive 100 patients. World J Surg 34:121-125

20. Ban D, Shimada K, Konishi M, et al (2012) Stapler and nonstapler closure of the pancreatic remnant after distal pancreatectomy: multicenter retrospective analysis of 388 patients. World J Surg 36:1866-1873

21. Hackert T, Hinz U, Pausch T, et al (2016) Postoperative pancreatic

fistula: We need to redefine grades B and C. Surgery 159:872-877
22. Tosoian JJ, Hicks CW, Cameron JL, et al (2015) Tracking early readmission after pancreatectomy to index and nonindex institutions: a more accurate assessment of readmission. JAMA surgery 150:152-158
23. Motoi F, Egawa S, Rikiyama T, et al (2012) Randomized clinical trial of external stent drainage of the pancreatic duct to reduce postoperative pancreatic fistula after pancreaticojejunostomy. Br J Surg 99:524-531
24. Wang H, Xiu D, Jiang B, et al (2014) Postoperative pancreatic fistula in distal pancreatectomy: experience from 1 institution. Pancreas 43:588-591
25. Bauhs JA, Vrieze TJ, Primak AN, et al (2008) CT dosimetry: comparison of measurement techniques and devices. Radiographics : a review publication of the Radiological Society of North America, Inc 28:245-253
26. Gaujoux S, Cortes A, Couvelard A, et al (2010) Fatty pancreas and increased body mass index are risk factors of pancreatic fistula after pancreaticoduodenectomy. Surgery 148:15-23
27. McMillan MT, Soi S, Asbun HJ, et al (2016) Risk-adjusted Outcomes of Clinically Relevant Pancreatic Fistula Following Pancreatoduodenectomy: A Model for Performance Evaluation. Annals of surgery 264:344-352
28. Ito A, Ebata T, Yokoyama Y, et al (2018) Ethanol ablation for refractory bile leakage after complex hepatectomy. Br J Surg 105:1036-1043

**Table 1.** Comparison of patients' characteristics based on the type of leakage (cavity and simple)

| Variable | Cavity type (*n*=22) | Simple type (*n*=107) | *p* Value |
|---|---|---|---|
| Patient factor | | | |
| Male | 14 (64) | 67 (63) | 0.928 |
| Age | 70 [40-83] | 66 [34-87] | 0.281 |
| BMI (kg/m$^2$) | 23.3 [19.1-28.0] | 22.7 [16.2-32.0] | 0.273 |
| DM | 3 (14) | 28 (26) | 0.210 |
| Diagnosis | | | |
| Pancreatic cancer | 8 (36) | 59 (55) | 0.108 |
| Periampullary cancer | 1 (5) | 7 (7) | |
| Distal bile duct cancer | 3 (14) | 11 (10) | |
| Duodenal cancer | 3 (14) | 11 (10) | |
| IPMN | 3 (14) | 9 (8) | |
| Other | 4 (18) | 10 (9) | |
| Operative findings | | | |
| PD | 12 (55) | 72 (67) | 0.253 |
| Soft pancreas | 20 (91) | 92 (86) | 0.736 |
| MPD ≤3 mm | 20 (91) | 71 (66) | 0.052 |
| Operation time (min) | 475 [202-620] | 463 [174-780] | 0.531 |
| Bleeding (mL) | 395 [60-1300] | 530 [20-2530] | 0.143 |
| Adjacent organ resection[a] | 8 (36) | 43 (40) | 0.738 |
| Fistula Risk Score[b] | | | |
| Intermediate or high | 12 (100) | 64 (86) | 0.344 |

Values are number (percentage) or median [range].

[a] Including portal vein, celiac axis, gastric, colon, and adrenal.

[b] Including only patients who underwent PD.

BMI, body mass index; DM, diabetes mellitus; PD, pancreaticoduodenectomy; MPD, main pancreatic duct.

1

**Table 2.** Comparison of postoperative findings between patients based on the type of leakage (cavity and simple)

| Variable | Cavity type (*n*=22) | Simple type (*n*=107) | *p* Value |
|---|---|---|---|
| Drain | | | |
| Amylase value on POD 1 (IU/L) | 5225 [998-60,000] | 2771 [21-60,000] | 0.023 |
| Amylase value on POD 3 (IU/L) | 4258 [144-60,000] | 1223 [20-52,319] | 0.003 |
| Amylase value on POD 7 (IU/L) | 1914 [21-60,000] | 1243 [27-60,000] | 0.215 |
| Fluid output on POD 7 (mL) | 50 [3-920] | 30 [3-1300] | 0.223 |
| Findings on POD 7 | | | |
| Albumin (g/dL) | 2.8 [2.1-3.9] | 2.9 [2.2-3.8] | 0.383 |
| Prealbumin (mg/dL) | 11.8 [6.6-18.8] | 13.5 [3.3-27.2] | 0.020 |
| WBC (/mm$^3$) | 9300 [5700-15,900] | 7900 [3200-15,600] | 0.062 |
| CRP (mg/dL) | 7.4 [2.1-23.0] | 5.8 [0.0-20.7] | 0.020 |
| Drain culture (positive for bacteria) | 3 (14) | 3 (3) | 0.062 |
| Postoperative course | | | |
| Antibiotics | 13 (59) | 27 (25) | 0.002 |
| Percutaneous drainage[a] | 9 (46) | 11 (14) | 0.002 |
| Pseudoaneurysm | 0 (0) | 1 (1) | 1.000 |
| Endoscopic nasopancreatic drain | 1 (5) | 1 (1) | 0.313 |
| Reoperation for POPF | 0 (0) | 2 (2) | 1.000 |
| Drain in place >3 weeks | 8 (36) | 41 (38) | 0.863 |
| Final grade B/C | 21 (95) | 68 (64) | 0.003 |
| Overall morbidity[b] | 14 (64) | 39 (36) | 0.018 |
| Overall mortality | 0 (0) | 1 (1) | 1.000 |
| Length of drain placement (days) | 34 [12-171] | 25 [7-86] | <0.001 |
| Length of hospital stay (days) | 39 [23-89] | 31 [4-106] | 0.006 |

Values are number (percentage) or median [range].

[a] Including repositioning of drain.

[b] Clavien-Dindo grade ≥2.

POD, postoperative day; WBC, white blood cell; CRP, C-reactive protein; POPF, postoperative pancreatic fistula.

**Table 3.** Univariate analysis of risk factors for pancreatic fistula grade B/C

| Variable | Pancreatic fistula | | |
|---|---|---|---|
| | Biochemical leakage (*n*=40) | Grade B/C (*n*=89) | *p* Value |
| Patient factor | | | |
| Sex (male) | 19 (48) | 62 (70) | 0.016 |
| Age (≥65 years) | 20 (50) | 57 (64) | 0.133 |
| BMI (≥25 kg/m$^2$) | 5 (13) | 22 (25) | 0.115 |
| DM (yes) | 12 (30) | 19 (21) | 0.287 |
| Pancreatic cancer (yes) | 21 (53) | 48 (54) | 0.880 |
| Operative findings | | | |
| Procedure (PD) | 12 (30) | 33 (37) | 0.435 |
| Pancreas texture (soft) | 34 (85) | 78 (88) | 0.682 |
| MPD (≤3 mm) | 25 (63) | 66 (74) | 0.133 |
| Operation time (>480 min) | 18 (45) | 37 (42) | 0.716 |
| Bleeding (>1000 mL) | 6 (15) | 15 (17) | 0.792 |
| Amylase value in drain | | | |
| POD 1 (>5000 IU/L) | 10 (25) | 34 (38) | 0.132 |
| POD 3 (>5000 IU/L) | 8 (20) | 21 (24) | 0.628 |
| POD 7 (>5000 IU/L) | 9 (23) | 17 (19) | 0.489 |
| Findings on POD 7 | | | |
| Albumin (<2.8 g/dL) | 15 (38) | 29 (33) | 0.586 |
| Prealbumin (<15 mg/dL) | 25 (63) | 57 (64) | 0.747 |
| WBC (>9000/mm$^3$) | 13 (33) | 40 (45) | 0.184 |
| CRP (>6 mg/dL) | 14 (35) | 50 (56) | 0.026 |
| Drain culture (positive for bacteria) | 0 (0) | 6 (7) | 0.176 |
| Fistulography (cavity type) | 1 (3) | 21 (24) | 0.003 |

Values are number (percentage).

BMI, body mass index; DM, diabetes mellitus; PD, pancreaticoduodenectomy; MPD, main pancreatic duct; POD, postoperative day; WBC, white blood cell; CRP, C-reactive protein.

**Table 4.** Multivariate analysis of risk factors for pancreatic fistula grade B/C

| | Odds ratio | 95% CI | *p* Value |
|---|---|---|---|
| Male | 2.7 | (1.2–6.0) | 0.015 |
| Cavity type in fistulography | 12.9 | (1.6–101.6) | 0.015 |

Values in parentheses are 95% confidence intervals.

**Figure legend**

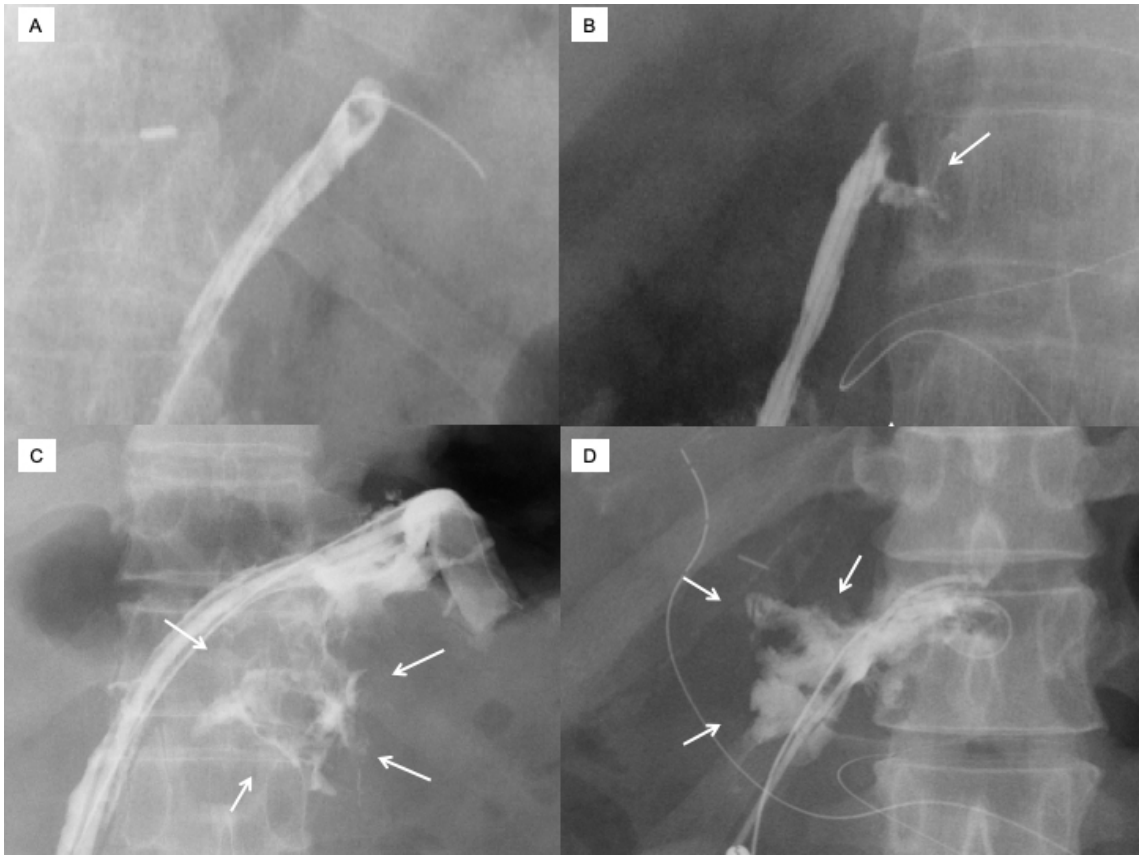
**Fig. 1** Classification of fistulography

**a.** Simple type of fistula after distal pancreatectomy. Fistulography shows only a simple tract. The contrast medium did not expand at the cut-edge of the pancreas.

**b.** Simple type of fistula after pancreaticoduodenectomy. Fistulography shows a simple tract with a small amount of outflow of contrast medium near the pancreaticojejunostomy.

**c.** Cavity type of fistula after distal pancreatectomy. Fistulography shows pooling of contrast medium at the cut-edge of the pancreas.

**d.** Cavity type of fistula after pancreaticoduodenectomy. Fistulography shows pooling of contrast medium at the cut-edge of the pancreas.




1